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Multi-dimensional population balance model development and validation for a twin screw granulation process

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ABSTRACT

In this study, a novel multi-component population balance model (PBM) for the twin-screw granulation (TSG) process was developed, taking into account the rate processes of aggregation, breakage, liquid addition, and consolidation. Interactions between multiple solid components (e.g. active pharmaceutical ingredient and excipient) and the amount of liquid were accounted for in quantifying the aggregation and breakage rates. Experimental data was obtained for the TSG process, whereby the effect of initial particle size distribution and liquid-to-solid ratios on key granule properties was studied. The data was used to estimate adjustable parameters in the proposed mechanistic kernels and to validate the calibrated process model as a predictive tool. The simulation results showed a good agreement with experimental data.

1. Introduction & objectives

Wet granulation is often used in pharmaceutical manufacturing as an intermediate step in the tablet-manufacturing process. While tablet manufacturing is primarily operated in a batch mode, continuous processing is being investigated for its potential advantages in cost, controllability, and scalability [1]. Currently, the design and control of pharmaceutical powder processes are primarily based on heuristic experimentation. To implement Quality by Design (QbD) in these processes, a design space must be defined such that the critical quality attributes (CQAs) of the product meet desired specification, if the process is operated within this space. In order to make the transition to continuous manufacturing, a better process understanding is needed to predict the effects of material and process parameters on CQAs. A model-based approach can be used to validate, optimize, and design these processes.

Continuous wet granulation processes can be categorized into four types: fluidized bed, high shear, drum, and twin screw granulation (TSG). TSG is well-suited to pharmaceutical processes for its optimal throughput, short residence times, design flexibility, and ability to mix ingredients [2,3]. Note that TSG is different from twin screw extrusion, where the granules fall from the open end of the screw conveyor in the TSG configuration, rather than being extruded through a die.

Population balance models (PBMs) can be used to track particle distributions as they evolve due to aggregation, breakage, and other rate processes. One-dimensional (1-D) PBMs are typically implemented, only considering variations in particle size. While these models are computationally inexpensive, they do not account for other particle properties, such as liquid content and porosity [4]. Particle liquid content strongly influences aggregation rates, and porosity is a CQA that affects the compactability of the granules [5,6]. A lumped-parameter approach was used to take advantage of the computation speed of 1-D PBMs while considering additional particle properties [7,8]. Previously, a multi-dimensional PBM was used to model TSG, demonstrating the theoretical effects of various process parameters [9]. This study used hypothetical values for unknown parameters within the model, qualitatively capturing experimental trends.

The ability to explain and predict experimental observations is of particular importance in the highly-regulated pharmaceutical industry. Few studies quantitatively relate PBMs to measured results. Parameter estimation has been performed by Ramachandran and Barton, who used a multidimensional PBM to compare optimization techniques [10]. In addition, Braumann et al. used response surface methodology to estimate rate parameters in a multidimensional model for batch granulation [11].

In this study, a two-dimensional (2-D) PBM for a continuous TSG process is presented to track particles size and liquid distributions along an axial coordinate, while taking into account the rate processes of aggregation, breakage, liquid addition, and consolidation, as well as powder flow. The lumped-parameter approach was used to track the liquid content and porosity of each particle size class.

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Experimental data was collected to measure the effect of the liquid-to-solid ratio on the product size distribution and porosity. This data was used to estimate unknown rate parameters in the model. Parameter estimation was performed for two liquid-dependent aggregation kernels to compare their abilities to match the experimental trends. The calibrated model was used to predict additional data points, thus quantifying the predictive capability of the model.

Additionally, a three-dimensional (3-D) PBM is presented that accounts for an additional solid component, representing an active pharmaceutical ingredient (API). A composition-dependent term was added to the aggregation kernel to simulate attractive or repulsive effects between the excipient and API.

1.1. Objectives

The purposes of this study are to:

- Present a multi-dimensional PBM framework for continuous TSG processes.
- Calibrate and validate the model using experimental data.
- Use the model to predict additional experimental results.

2. Experimental methods

The experimental data was originally published in El Hagrasy et al. [2], which provides additional details on the experimental set-up and analytical methods. Product size distributions and porosity data were collected from a continuously-operated TSG in order to validate the model. A Thermo Pharma 16 TSG, 40:1 L:D, Thermo Fisher Scientific, Karlsruhe, Germany, was used to produce the granules used in the study. The screw configuration of the granulator with the sequence of elements from the drive end was 3 spacer elements, 16 conveyer elements, 5 kneading elements, and 8 conveyer elements.

A formulation of impalpable grade lactose (73.5%), Avicel PH101 (20%), hypromellose (5%), and Ac-Di-Sol (1.5%) was fed at a constant rate of 4 kg/h. The screw speed was fixed at 400 rpm. Water was used as the binding liquid, and the liquid-to-solid ratio was varied from 0.15 to 0.35. Particle size analysis of the raw material was performed using laser light diffraction (Malvern Mastersizer 2000, Malvern Instruments, Westborough, MA), and this data was used as an input to the model.

The process was allowed to reach a steady state, and the granulated product was collected for analysis. Sieve analysis was used to measure the granule size distributions, with sieve trays from 45 μm to 8 mm. The granule porosity of the 1–1.4 mm size class was measured using a GeoPyc Density Analyzer. The residence time was measured by feeding a pulse of dye to the TSG. Product samples were collected over time and analyzed by color. The arithmetic mean residence time of 9.9 s was used to estimate the average axial velocity within the granulator, and this value was used in the model.

3. Model development

As shown in Fig. 1, the twin-screw granulator can be divided into three axial zones. In the first zone, dry particles are added, and mixing occurs, but the particles do not begin to aggregate. The second zone is the liquid addition zone, where liquid binder is added to the particles. Aggregation begins in this zone. The final zone is the wet massing zone, where the wet particles continue to aggregate and consolidate. The wet massing zone consists of 5 kneading blocks followed by a length of screw conveyor [2]. The lengths of the three zones were 8 cm, 8 cm and 16 cm, respectively. In order to model this granulator, a compartment approach was used, dividing the liquid addition and wet massing zones into three equally spaced regions. The premixing zone was neglected because the effects of this zone on the granule attributes were assumed to be negligible. It was assumed that the residence time in each of the three compartments was equal and constant. Future work will involve characterizing the size of the liquid distribution region using multi-scale modeling and experimental validation.

A dynamic, two-dimensional PBM was developed to represent twin screw granulation processes. As shown in Eq. 1, the particle distribution was tracked at three locations within the granulator over time from start-up until a steady state was reached.

$$\frac{dF(s,z,t)}{dt} = \mathfrak{R}_{\text{agg}}(s,z,t) + \mathfrak{R}_{\text{break}}(s,z,t) + \dot{F}_{\text{in}}(s,z,t) - \dot{F}_{\text{out}}(s,z,t). \qquad (1)$$

F represents the number of particles in each bin, and the bins were defined by the solid volume of each particle, s, and the spatial compartment, z. $\mathfrak{R}_{\text{agg}}$ and $\mathfrak{R}_{\text{break}}$ represent the net aggregation and breakage rates, respectively. The inlet and outlet flow rates for each compartment are given by $\dot{F}_{\text{in},}$ and $\dot{F}_{\text{out}}$.

Eq. 1 alone only accounts for the amount of solid in the granule. However, other granule properties such as liquid content and porosity are known to have strong effects on aggregation and breakage rates. To simulate these properties, a lumped-parameter approach was used [7,8], making the assumption that all particles of the same solid content and position have the same porosity and liquid content. Eqs. 2 and 3 were developed to track the liquid and gas content of each bin in each compartment.

$$\begin{aligned}\frac{d}{dt}(F(s,z,t)l(s,z,t)) &= \mathfrak{R}_{\text{liq,agg}}(s,z,t) + \mathfrak{R}_{\text{liq,break}}(s,z,t) + \dot{F}_{\text{in}}(s,z,t)l_{\text{in}}(s,z,t) \\ &\quad - \dot{F}_{\text{out}}(s,z,t)l(s,z,t) + F(s,z,t)\dot{l}_{\text{add}}(s,z,t)\end{aligned} \qquad (2)$$

$$\begin{aligned}\frac{d}{dt}(F(s,z,t)g(s,z,t)) &= \mathfrak{R}_{\text{gas,agg}}(s,z,t) + \mathfrak{R}_{\text{gas,break}}(s,z,t) + \dot{F}_{\text{in}}(s,z,t)g_{\text{in}}(s,z,t) \\ &\quad - \dot{F}_{\text{out}}(s,z,t)g(s,z,t) - F(s,z,t)\dot{g}_{\text{cons}}(s,z,t)\end{aligned} \qquad (3)$$

The volumes of liquid and gas, per particle, are given by l and g, respectively. Similar to Eq. 1, these equations account for axial flow between compartments, the inlet and outlet streams, aggregation and breakage. The net change in liquid and gas volumes due to aggregation and breakage are represented by $\mathfrak{R}_{\text{liq,agg}}$, $\mathfrak{R}_{\text{liq, break}}$, $\mathfrak{R}_{\text{gas,agg}}$,and $\mathfrak{R}_{\text{gas,break}}$. The lumped-parameter equations also account for the liquid added to the particles and consolidation. $\dot{l}_{\text{add}}$ represents the volumetric rate of liquid addition, per particle, and$\dot{g}_{\text{cons}}$ is the rate of consolidation.

The lumped-parameter approach was used because it combines the computational speed of a 1-D PBM with the ability to simulate multiple

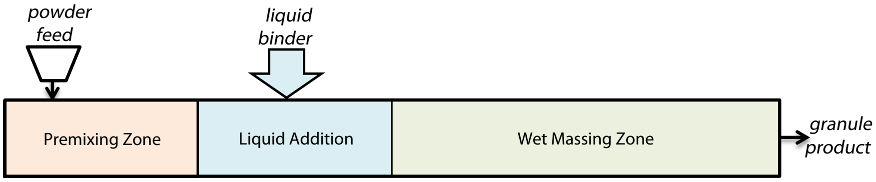

Fig. 1. Three regions of the twin-screw granulator based on the experimental setup.